Oncology and Translational Medicine
DOI 10.1007/s10330-015-0068-x

April 2015, Vol. 1, No. 2, P51–P57

REVIEW ARTICLE

Role of radiation therapy in the management of stage III non-small cell lung cancers: current status and controversies

Wen Feng[1, 2], Xiaolong Fu[3] (✉)

[1] Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China
[2] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China
[3] Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

Abstract

The treatment of stage III non-small cell lung cancer (NSCLC) consisting of the heterogeneous stage subsets remains a challenge. Overall, it has been gradually recognized that radiation therapy (RT) plays a crucial role in the management of stage III NSCLC. One superior sulcus tumors are the subset for which the trimodality treatments are clearly preferred. One subset of stage III NSCLC has a minimal disease burden with microscopic pN2 disease or with discrete pN2 involvement identified preoperatively, thus technically could undergo a surgical resection. For the incidentally found pN2 disease after complete surgery (IIIA-1, IIIA-2), the value of postoperative radiotherapy (PORT) has been recognized by a reassessment based on new data. However, doubt persists regarding how to define the clinical target volume for PORT. For the discrete pN2 involvement identified preoperatively (a selected part of IIIA-3), induction chemoradiation therapy (CRT) before surgery may yield a survival advantage, although the phase III randomized trials in this issue are not conclusive. The other major subset of stage III NSCLC is the infiltrative stage III NSCLC with N2 or N3 nodal disease (IIIA-3, IIIA-4, and IIIB), for which concurrent CRT is considered as the current standard of care. The potential role of radiation dose escalation/acceleration has been proposed; however, the optimal dose fractionation remains an important unresolved question. Additionally, the role of prophylactic cranial irradiation for stage III patients with high risk of brain metastasis is worth of further assessment. Moreover, how to integrate molecular targeted therapy with RT, as well as whether they had a role in stage III diseases, are other controversies actively under study in ongoing trials. This review specifically describes the updated role of RT in multimodal approach to treat stage III NSCLC and the controversies regarding these results in various situations.

Received: 2 February 2015
Revised: 15 February 2015
Accepted: 5 March 2015

Key words: non-small cell lang cancer (NSCLC); stage III; radiotherapy; chemoradiotherapy

Stage III non-small cell lung cancer (NSCLC) comprises a heterogeneous group of patients with distinct clinical subsets [1]. Several distinct subgroups of patients are identifiable and may be classified using these characteristics [2]: (1) IIIA-0 (T3N1 or T4N0-1), tumors with locoregional extension without N2 involvement; (2) IIIA-1, incidental pN2 metastases found in the final pathological examination of the surgical specimen; (3) IIIA-2, mediastinal nodal metastases identified intraoperatively; (4) IIIA-3, single-station or multistation N2 involvement demonstrated by preoperative assessment using mediastinoscopy, other nodal biopsy, or positron emission tomography/computed tomography (PET/CT) imaging; (5) IIIA-4, bulky or fixed N2 involvement at imaging; and (6) IIIB, tumors with N3 nodal involvement. This classification system has been the basis for further discussions on how to approach treatment of patients with stage III NSCLC. In the present review, we evaluate the role of radiation therapy (RT) in the management of superior sulcus NSCLC (special issue in stage IIIA-0). We also examine a surgically based combined modality approach for tumors in stage IIIA-1, IIIA-2, and a subset of IIIA-3, and an optimal RT-based combined modality approach for patients with stage IIIA-3, IIIA-4, and IIIB NSCLC.

✉ Correspondence to: Xiaolong Fu. Email: xlfu1964@126.com

Management of superior sulcus tumors (T3-4N0-1)

Superior sulcus (SS) NSCLC originates in the apex of the lung. Invasion of the chest wall and, potentially, adjacent vital structures including the brachial plexus, vertebral body, and subclavian vessels makes surgical resection challenging. Increasing data have suggested that a multimodality approach, involving induction chemoradiation therapy (CRT) and surgical resection, appeared to be optimal [3–5]. The Southwest Oncology Group (SWOG) published the results of Trial 9416, a prospective phase II clinical trial involving induction CRT (two cycles of cisplatin and etoposide concurrent with 45 Gy RT) followed by surgical resection. With 110 eligible patients with T3-4N0-1 SS NSCLC, it demonstrated that disease recurrence occurs primarily at distant sites. The 5-year overall survival (OS) was 44%. In the patients with a complete resection following induction therapy, the 5-year OS was 54% [3]. The Japan Clinical Oncology Group 9806 trial, using a similar therapeutic approach (induction therapy with mitomycin/vindesine/cisplatin combined with 45 Gy of RT followed by surgery), resulted in a 5-year OS of 56% [4]. These results led to acceptance of trimodality therapy for T3-4N0-1 SS NSCLC as the standard of care. However, systemic failure has been the major contributor to long-term risk of death in both trials [3–4]. The SWOG S0220 was a phase II trial to determine the feasibility of treating SS tumors with induction CRT and definitive resection, followed by consolidation docetaxel. This study failed to achieve its primary end point. Whether postoperative consolidation therapy contributes to efficacy remains unclear, but distant recurrence continues to be a major problem in this subset, particularly brain-only relapse [5].

In summary, in patients with SS tumors, a thorough preoperative evaluation is recommended to assess the resectability of the tumor. Involvement of N2 lymph nodes, contralateral N3 lymph nodes, > 50% vertebral body, esophagus, trachea, and/or metastatic disease represent negative prognostic factors and should generally be considered a contraindication to surgery [3–6]. In patients with an unresectable SS tumor, definitive concurrent CRT is suggested. In patients with a potentially resectable SS tumor, it is suggested that induction concurrent CRT be given prior to resection. In the absence of evidence of progressive or metastatic disease at evaluation after induction therapy, surgical resection is warranted. If patients do not qualify for surgery, they should complete their definitive course of CRT [6]. Based on these phase II clinical trials, the RT dose used in the induction setting has historically been limited to 40–45 Gy administered in daily fractions of 1.8–2.0 Gy [3–5]. Radiation targets include the primary tumor and ipsilateral supraclavicular area, but not the mediastinum or hilum [3–5].

Perspectives regarding a surgically based combined modality approach

For patients with suspected N2 involvement, the importance of careful and appropriate stage evaluation should be emphasized. It is recommended that the treatment plan be made collaboratively by a multidisciplinary team. The surgical resection should consist of a lobectomy rather than a non-anatomic wedge resection [7–8]. The definition of complete resection requires that free resection margins proved microscopically, a systematic and standardized nodal assessment, no extracapsular nodal extension of the tumor, and that the highest mediastinal node removed be negative [9]. The discussion that follows assumes adherence to these principles.

Generally, for incidentally found pN2 disease after complete resection (IIIA-1, IIIA-2), the role of postoperative radiotherapy (PORT) has been recognized by a reassessment based on new data [10–13]. However, the method of defining the PORT clinical target volume (CTV) for 3-dimensional conformal radiation therapy (3D-CRT) of completely resected NSCLC patients is still unclear [14]. For discrete pN2 involvement identified preoperatively (a selected group of IIIA-3), it is suggested that surgical resection can be considered after induction chemotherapy in patients who are likely candidates for lobectomy upfront [15–16]. However, despite several promising results, the role of induction CRT is still debatable and further studies on induction CRT are warranted.

Postoperative radiotherapy for occult N2 NSCLC after complete resection

Phase III randomized trials and meta-analyses have conclusively demonstrated that cisplatin-containing doublets-based postoperative chemotherapy (POCT) has a positive impact on OS in postoperative stage II and III NSCLC [7–8]. In a meta-analysis of these trials, the NSCLC Meta-analyses Collaborative Group confirmed an OS benefit for adjuvant chemotherapy for operable NSCLC, with an absolute improvement in survival of 4% at 5 years [17]. However, even after complete resection and POCT, 20% to 40% of patients still have a risk of local-regional failure [18]. PORT should be an integral component of multidisciplinary treatment for patients with pN2 disease found incidentally after complete resection [8]. Although the PORT meta-analysis failed to demonstrate a survival benefit of PORT in completely resected patients with mediastinal involvement [19], there are some problems that must be considered and studied in an era of modern PORT techniques. There has been new information based

both on subgroup analyses from a prospective adjuvant trial [10] and a large population-based outcome analysis [11] suggesting a possible survival benefit of PORT in stage IIIA (pN2) disease. Recently, a review of the National Cancer Database indicated that modern PORT appears to confer an additional 5% survival advantage beyond that achieved with adjuvant chemotherapy alone [13]. The National Comprehensive Cancer Network and American College of Chest Physicians guidelines [7–8] recommend that PORT is generally administered in a sequential fashion following completion of adjuvant chemotherapy.

Thus, the available evidence suggests that patients with completely resected pN2 disease be strongly considered for PORT, especially using modern radiation treatment methods and in combination with adjuvant chemotherapy. However, there are still doubts regarding the definition of the PORT CTV for 3D-CRT in completely resected NSCLC patients. Most studies in the PORT meta-analysis [19], in which an excess mortality was observed, used large radiation field sizes. Miles *et al* attempted to estimate the field size dependence of RT-induced mortality and tumor control in a postoperative setting [20]. It has been shown that RT-induced mortality is strongly dependent on field size, which may partly offset the OS benefit afforded by PORT. Anatomic and clinical findings, including the distribution of pathologic nodal involvement at the time of surgery, and postoperative patterns-of-failure studies provide guidance to optimize design fields based on the most likely sites of locoregional failure [21–24]. It has been suggested that ipsilateral superior mediastinal recurrences dominate for right-sided tumors, whereas left-sided tumors frequently involve the bilateral superior mediastinum [23–24], which should be taken into consideration in clinical practice.

Induction chemoradiation therapy for pN2 NSCLC identified preoperatively

From the currently available data, it is evident that preoperative chemotherapy should be recommended if surgical resection is planned in potentially resectable stage IIIA (pN2) disease [7–8]. Recently, a systematic review and meta-analysis of individual participant data, based on mainly stage IB-IIIA, showed that preoperative chemotherapy significantly improved OS, time to distant recurrence, and recurrence-free survival in resectable NSCLC [25]. The findings suggest this is a valid treatment option for most of these patients.

Currently, the role of induction CRT in stage IIIA (pN2) NSCLC remains unclear. Recently, the West Japan Thoracic Oncology Group published a phase III study of induction CRT (2 cycles of docetaxel and carboplatin plus concurrent 40 Gy RT) compared to induction chemotherapy alone before surgery in patients with stage IIIA (pN2) NSCLC [26]. The results demonstrated that the addition of RT to an induction chemotherapy regimen for stage IIIA (pN2) NSCLC conferred better local control and improved tumor downstaging rates without additional significant adverse events. However, this favorable local control did not translate to a significant survival difference. Similarly, a recent trial from Japan on induction CRT followed by surgery for patients with pN2 NSCLC indicated that it was superior to induction chemotherapy in terms of survival outcome of patients with pN2 disease [27]. Unfortunately, this trial was limited by its lack of a randomized design and small sample size. In conclusion, it is still debatable whether the addition of radiation is beneficial to induction chemotherapy, warranting further studies on the role of induction CRT.

Perspectives regarding the RT-based combined modality approach

For potentially resectable stage IIIA (pN2) disease (IIIA-3), definitive concurrent CRT generally provides a similar survival outcome as induction therapy followed by surgery in an unselected patient population with pathologically confirmed N2 disease [15–16]. For infiltrative stage III NSCLC with N2 or N3 nodal disease (IIIA-4, IIIB), concurrent CRT has become the standard of care. The role of additional chemotherapy, either as induction chemotherapy or consolidative chemotherapy, at the completion of chemoradiation has not been well elucidated. In addition, issues of optimal radiation fractionation should continue to be explored.

Concurrent chemoradiation therapy

Over the last two decades, based on several randomized trials and meta-analyses, concurrent CRT has become the standard approach, leading to an improvement in survival [28–29]. Radiation Therapy Oncology Group (RTOG) trial 9410 was a three-arm randomized trial comparing sequential chemotherapy and a thoracic RT regimen (once daily to 63 Gy) with two concurrent CRT regimens (concurrent once-daily RT to 63 Gy and concurrent twice-daily RT to 69.6 Gy) [28]. The results showed that concurrent delivery of cisplatin-based chemotherapy with thoracic RT conferred a long-term survival benefit compared with the sequential delivery of these therapies. In 2010, the NSCLC collaborative group demonstrated a significant survival advantage with concurrent CRT compared with sequential treatment (hazard ratio: 0.84) with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years [29]. However, even with such definitive concurrent CRT, both local and distant failures continue to be major problems, indicating a need to improve both local and distant control of this disease [28–29], which would hopefully translate into survival improvements.

Role of additional chemotherapy before or after concurrent CRT

With fewer cycles and, in some cases, lower doses of chemotherapy delivered in the concurrent setting, several studies have assessed whether delivering further chemotherapy, either before (induction) or after (consolidation) concomitant treatment, would improve survival by reducing the risk of distant relapse.

The Cancer and Leukemia Group B (CALGB) has reported a phase III trial (CALGB 39801) comparing induction chemotherapy with two cycles of carboplatin and paclitaxel followed by concurrent CRT with initial concurrent therapy in patients with unresectable stage III disease [30]. This large cooperative group trial failed to confirm earlier phase II results, with somewhat disappointing median survival times of 12 months for the initial concurrent regimen and 14 months for induction followed by concurrent therapy ($P = 0.3$).

The SWOG conducted a phase II trial to evaluate the benefit of adding three cycles of consolidation docetaxel following concurrent CRT in patients with stage IIIB NSCLC [31]. Median survival was 26 months and the 3-year OS rate was 37%. However, the Hoosier Oncology Group attempted to confirm the SWOG results in a phase III trial [32] and found no survival benefit for consolidation therapy with docetaxel but a significant increase in toxicity. Recently, a pooled analysis based on the literature failed to provide evidence that consolidation chemotherapy yields a survival benefit for locally advanced NSCLC (LA-NSCLC), with a pooled median OS of 19.0 months compared to 17.9 months, $P = 0.40$ [33]. The preliminary results of the phase III study (CCheIN trial) on the role of consolidation chemotherapy after concurrent CRT in inoperable stage III NSCLC were reported at the 2014 American Society of Clinical Oncology (ASCO) annual meeting [34] and suggested that consolidation chemotherapy with cisplatin/docetaxel after concurrent CRT did not prolong progression-free survival and OS in stage III NSCLC.

Therefore, the role of additional chemotherapy, either as induction or consolidative chemotherapy, at the completion of CRT has not been well elucidated, and current guidelines continue to recommend concurrent CRT alone for the treatment of inoperable stage III NSCLC.

Dose escalation and altered fractionation

The standard treatment for LA-NSCLC is recognized as concurrent CRT with curative intent [7-8]. There is ample evidence that involved field irradiation can be employed in patients with LA-NSCLC [35–37]. The standard radical concurrent RT schedule is 60-66 Gy delivered once daily in 1.8-2.0 Gy fractions [7-8]. However, the optimal radiation dose and fractionation schema to be given concurrently with chemotherapy remains controversial. The RTOG conducted a phase III study (RTOG 0617) in which the radiation dose was escalated from 60 Gy to 74 Gy with concurrent carboplatin plus paclitaxel with or without cetuximab for patients with stage III NSCLC. The preliminary data of RTOG 0617 showed that 74 Gy administered in 2 Gy fractions with concurrent chemotherapy was not more effective than 60 Gy with concurrent chemotherapy, and might even be potentially harmful [38]. This study raised many questions about the controversial issues of safety and efficacy of dose escalation in stage III NSCLC. Thus, for now, dose escalation using conventional fractionation should not be used outside any clinical trial.

Randomized trials assessing hyperfractionated and/or accelerated RT over conventionally fractionated RT in lung cancer have yielded conflicting results on the benefits for locoregional control and OS. Recently, an individual patient data meta-analysis of ten randomized trials comparing hyperfractionated and/or accelerated RT to conventional fractionation confirmed the advantage of altered RT fractionation, increasing absolute 5-year survival benefit by 2.5% in NSCLC (HR 0.88, 95% CI 0.8–0.97, $P = 0.009$) [39].

A retrospective study from 4 centers in the UK showed respectable results for NSCLC patients treated with an accelerated hypofractionated RT (55 Gy in 20 fractions over 4 weeks) regimen, suggesting that there is room for dose escalation within shorter schedules and schedules with higher doses per fraction [40]. The introduction of stereotactic body radiation therapy (SBRT) might provide a feasible RT technique for LA-NSCLC by precisely delivering higher biological equivalent doses [41–42]. A recent prospective single institution study showed that combining conventional CRT with salvage SBRT was both feasible and tolerable [41]. The local control rates in this study were promising. However, the unique aspect of this strategy was in its selection of patients with limited residual disease within the site of the primary tumor. Another retrospective study also confirmed that dose escalation with an SBRT boost following external beam RT was a possible and generally tolerated treatment option for patients with LA-NSCLC [42]. The incorporation of PET imaging is another strategy to escalate the RT dose, using an integrated boost to regions of high fluorodeoxyglucose (FDG) uptake [43]. Dose escalation and redistribution based on functional imaging is at the heart of the EU Framework Programme 7-funded PET Boost trial [43]. The overall treatment dose is escalated by increasing the dose-per-fraction until specified dose constraints are met. Patients were randomized to receive the standard regimen (66 Gy given in 24 fractions of 2.75 Gy) with an integrated boost either to the primary tumor as a whole or to the 50% SUVmax area of the primary tumor based on the pre-treatment PET/CT scan. This study showed the feasibility of creating dose-

escalation plans using an integrated boost to the primary tumor or regions of high FDG uptake while maintaining pre-defined dose constraints [43].

Practically, dose escalation is challenging owing to the tolerance of normal tissues. Recently, a number of innovative changes have occurred in radiotherapeutic planning and delivery, which may give an impetus to explore the issues of dose escalation and acceleration [43–49]. Firstly, intensity-modulated radiation therapy (IMRT) has been shown to be a promising technique for facilitating safe dose escalation [44–45]. One study demonstrated the potential benefits of IMRT and a non-coplanar field, which dramatically reduced the doses received by the heart when the tumor is located in the lower and middle lobes [44]. A follow-up retrospective report of 151 NSCLC patients treated with IMRT showed an 8% incidence of grade ≥3 treatment-related pneumonitis at 12 months, compared with 23% for a similar group of 222 patients treated with 3D-CRT [45]. IMRT has shown promise in dosimetric modeling studies for reducing normal tissue complication probability, thus allowing for dose escalation in NSCLC patients. Secondly, the implementation of better functional imaging in RT treatment planning, such as PET image-guided dose escalation, now allows us to deliver higher doses to anatomically and biologically defined target volumes, while better sparing normal tissues [43]. Target delineation with PET allows integrated dose painting to high-risk regions with minimal increased dosage to normal tissues, potentially translating into improved local control. Thirdly, several individualized radiation dose prescription studies have evaluated the feasibility of escalating the dose based on individualized normal tissue dose constraints [46–47]. This strategy, known as individualized accelerated radiotherapy (INDAR), has been demonstrated to be feasible with acceptable toxicity and promising results [48]. Recently published phase II data of 137 patients with stage III NSCLC treated with INDAR and concurrent chemotherapy showed encouraging OS rates (median survival 25 months, 2-year OS 52.4%) with acceptable rates of acute and late toxicity [49].

Prophylactic cranial irradiation for stage III NSCLC

The brain is a frequent site of first failure in stage III disease and the cumulative incidence of brain metastases (BM) increases as the patient's survival improves [50–51]. BM causes considerable morbidity and disability, making the prevention or delay of brain relapse of significant importance. A number of studies have investigated the role of prophylactic cranial irradiation (PCI) in LA-NSCLC. The RTOG 0214 study randomly assigned patients with stage III NSCLC without disease progression after treatment to either PCI (30 Gy in 15 fractions of whole-brain RT) or observation. The study showed that patients with LA-NSCLC who did not receive PCI were 2.52 times more likely to develop BM than patients who received PCI [51]. However, PCI is not recommended as a standard therapy because of concerns of long-term toxicity and lack of a proven survival benefit [8]. It has been hypothesized that PCI should be administered to patients at high risk for BM. More recently, a randomized phase III trial found that PCI prolonged disease-free survival, decreasing the rate of BM among patients with completely resected stage IIIA (pN2) NSCLC and with a high risk of BM after adjuvant chemotherapy [52]. Thus, future studies assessing PCI should focus on these high-risk patients and minimizing the risks of PCI with selective RT planning.

Targeted therapy in stage III NSCLC

The clinical importance of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) and inhibitors of the anaplastic lymphoma kinase (ALK) in stage IV disease poses an important question as to whether these agents play any role in stage III disease. However, there are little nature data regarding the incorporation of these new anticancer agents in patients with stage III NSCLC harboring activating mutations. Currently, the effect of concurrent EGFR TKIs and definitive RT is under clinical investigation. A phase III randomized trial comparing concurrent erlotinib and thoracic RT with concurrent CRT (two cycles of cisplatin and etoposide concurrent with once-daily 60–66 Gy RT) in inoperable stage III EGFR mutation-positive NSCLC is ongoing. The use of a EGFR TKI (erlotinib) or ALK inhibitor (crizotinib) as an induction regimen prior to standard concurrent CRT in patients with stage III NSCLC positive for either a EGFR mutant or ALK fusion is also under investigation in the randomized phase II trial (RTOG 1210/Alliance 31101). These ongoing prospective trials will hopefully shed more light on this important issue.

Consensus and future directions

The role of induction CRT has been recognized as a standard of care for patients with stage IIIA-0 NSCLC with SS tumors. For incidentally found pN2 disease fafter complete resection (IIIA-1, IIIA-2), the role of PORT has been confirmed by a reassessment based on new data. However, it is still not clear how the PORT target volume for 3D-CRT in completely resected NSCLC patients should be defined. For patients with with the discrete pN2 disease, the role of induction CRT remains debatable until the final data of the prospective study are available. Concurrent CRT remains the standard treatment for most LA-NSCLC patients with good performance status. Treatment intensification by adding induction or consolida-

tion chemotherapy has not yet demonstrated any survival benefit over concurrent CRT alone. Based on available information, concurrent CRT remains the standard care for management of stage III NSCLC patients with EGFR mutations. Ongoing prospective studies are exploring the role of targeted therapy in stage III NSCLC. Involved field RT is recommended in a concurrent RT setting. The standard definitive concurrent RT schedule is 60–66 Gy delivered with once-daily 1.8–2.0 Gy fractions. However, the optimal radiation dose and fractionation schema to be administered concurrently with chemotherapy remains unclear. PCI has been proved to decrease the rate of BM but did not improve OS. Thus, PCI is not recommended as standard therapy because of concern for long-term toxicity and lack of a proven survival benefit. However, the impact of PCI for stage III patients with high-risk BM risk is worthy of further assessment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Andre F, Grunenwald D, Pignon JP, *et al.* Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol, 2000, 18: 2981–2989.
2. van Meerbeeck JP, Surmont VF. Stage IIIA-N2 NSCLC: a review of its treatment approaches and future developments. Lung Cancer, 2009, 65: 257–267.
3. Rusch VW, Giroux DJ, Kraut MJ, *et al*. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol, 2007, 25: 313–318.
4. Kunitoh H, Kato H, Tsuboi M, *et al*. Japan Clinical Oncology Group. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. J Clin Oncol, 2008, 26: 644–649.
5. Kernstine KH, Moon J, Kraut MJ, *et al*. Trimodality therapy for superior sulcus non-small cell lung cancer: Southwest Oncology Group-Intergroup Trial S0220. Ann Thorac Surg, 2014, 98: 402–410.
6. Kozower BD, Larner JM, Detterbeck FC, *et al*. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 2013, 143: 369S–399S.
7. Ramnath N, Dilling TJ, Harris LJ, *et al.* Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 2013, 143: 314S–340S.
8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small-cell lung cancer, v.4.2014. Http: www.nccn.org.
9. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer, 2005, 49: 25–33.
10. Douillard JY, Rosell R, De Lena M, *et al*. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: The Adjuvant Navelbine International Trialist Association (ANITA) randomized trial. Int J Radiat Oncol Biol Phys, 2008, 72: 695–701.
11. Lally BE, Zelterman D, Colasanto JM, *et al.* Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol, 2006, 24: 2998–3006.
12. Billiet C, Decaluwé H, Peeters S, *et al*. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol, 2014, 110: 3–8
13. Mikell JL, Gillespie TW, Hall WA, *et al*. Post-operative radiotherapy (PORT) is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the national cancer data base. J Thorac Oncol, 2015,10: 462–471.
14. Spoelstra FO, Senan S, Le Péchoux C, *et al.* Variations in target volume definition for postoperative radiotherapy in stage III nonsmall-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys, 2010, 76: 1106–1113.
15. van Meerbeeck JP, Kramer GW, Van Schil PE, *et al*. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst, 2007, 99: 442–450.
16. Albain KS, Swann RS, Rusch VW, *et al*. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet, 2009, 374: 379–386.
17. Arriagada R, Auperin A, Burdett S, *et al*. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet, 2010, 375: 1267–1277.
18. Wagner H Jr. Postoperative adjuvant therapy for patients with resected non-small-cell lung cancer: still controversial after all these years. Chest, 2000, 117: 110S–118S.
19. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for nonsmall cell lung cancer. Cochrane Database Syst Rev, 2005, 18: CD002142.
20. Miles EF, Kelsey CR, Kirkpatrick JP, *et al*. Estimating the magnitude and field-size dependence of radiotherapy-induced mortality and tumor control after postoperative radiotherapy for non-small-cell lung cancer: calculations from clinical trials. Int J Radiat Oncol Biol Phys, 2007, 68: 1047–1052.
21. Hata E, Hayakawa K, Miyamoto H, *et al.* Rationale for extended lymphadenectomy for lung cancer. Theor Surg, 1990, 5: 19–25.
22. Giraud P, De Rycke Y, Minet P, *et al.* Estimation of the probability of mediastinal involvement: A statistical definition of the clinical target volume for 3-dimensional conformal radiotherapy in non-small-cell lung cancer? Cancer Radiother, 2001, 5: 725–736.
23. Feng W, Fu XL, Cai XW, *et al*. Patterns of local-Regional failure in completely resected stage IIIA (N2) non-small cell lung cancer cases: implications for postoperative radiation therapy clinical target volume design. Int J Radiat Oncol Biol Phys, 2014, 88: 1100–1107.
24. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys, 2006, 65: 1097–1105.
25. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet, 2014, 383: 1561–1571.

26. Katakami N, Tada H, Mitsudomi T, *et al.* A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). Cancer, 2012, 118: 6126–6135.
27. Toyooka S, Kiura K, Shien K, *et al*. Induction chemoradiotherapy is superior to induction chemotherapy for the survival of non-small-cell lung cancer patients with pathological mediastinal lymph node metastasis. Interact Cardiovasc Thorac Surg, 2012, 15: 954–960.
28. Curran WJ Jr, Paulus R, Langer CJ, *et al.* Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst, 2011, 103: 1452–1460.
29. Aupérin A, Le Péchoux C, Rolland E, *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol, 2010, 28: 2181–2190.
30. Vokes EE, Herndon JE 2nd, Kelley MJ, *et al*. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol, 2007, 25: 1698–1704.
31. Gandara DR, Chansky K, Albain KS, *et al*. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB nonsmall-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol, 2003, 21: 2004–2010.
32. Hanna N, Neubauer M, Yiannoutsos C, *et al*. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III nonsmall-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol, 2008, 26: 5755–5760.
33. Tsujino K, Kurata T, Yamamoto S, *et al*. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A Pooled Analysis of the Literature. J Thorac Oncol, 2013, 8: 1181–1189.
34. Park K, Ahn YC, Ahn JS, *et al*. A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III nonsmall cell lung cancer (CCheIN). J Clin Oncol, 2014, 32: 7500.
35. Bradley J, Graham MV, Winter K, *et al.* Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable nonsmall-cell lung carcinoma. Int J Radiat Oncol Biol Phys, 2005, 61: 318–328.
36. Rosenzweig KE, Sura S, Jackson A, *et al.* Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol, 2007, 25: 5557–5561.
37. Yuan S, Sun X, Li M, *et al*. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol, 2007, 30: 239–244.
38. Bradley JD, Paulus R, Komaki R, *et al*. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol, 2015, 16: 187–199.
39. Mauguen A, Le Péchoux C, Saunders MI, *et al.* Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol, 2012, 30: 2788–2797.
40. Din OS, Harden SV, Hudson E, *et al.* Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: results from 4 UK centres. Radiother Oncol, 2013, 109: 8–12.
41. Feddock J, Arnold SM, Shelton BJ, *et al*. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: a prospective study. Int J Radiat Oncol Biol Phys, 2013, 85: 1325–1331.
42. Karam SD, Horne ZD, Hong RL, *et al.* Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer. Radiat Oncol, 2013, 8: 179.
43. van Elmpt W, De Ruysscher D, van der Salm A, *et al.* The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. Radiother Oncol, 2012, 104: 67–71.
44. Chapet O, Khodri M, Jalade P, *et al*. Potential benefits of using non coplanar field and intensity modulated radiation therapy to preserve the heart in irradiation of lung tumors in the middle and lower lobes. Radiother Oncol, 2006, 80: 333–340.
45. Yom SS, Liao Z, Liu HH, *et al*. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys, 2007, 68: 94–102.
46. van Baardwijk A, Bosmans G, Boersma L, *et al.* Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. Int J Radiat Oncol Biol Phys, 2008, 71: 1394–1401.
47. van Baardwijk A, Bosmans G, Bentzen SM, *et al*. Radiation dose prescription for non-small-cell lung cancer according to normal tissue dose constraints: an in silico clinical trial. Int J Radiat Oncol Biol Phys, 2008, 71: 1103–1110.
48. van Baardwijk A, Wanders S, Boersma L, *et al*. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. J Clin Oncol, 2010, 28: 1380–1386.
49. van Baardwijk A, Reymen B, Wanders S, *et al.* Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer. Eur J Cancer, 2012, 48: 2339–2346.
50. Mamon HJ, Yeap BY, Janne PA, *et al*. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. J Clin Oncol, 2005, 23: 1530–1537.
51. Gore EM, Bae K, Wong SJ, *et al*. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol, 2011, 29: 272–278.
52. Li N, Zeng ZF, Wang SY, *et al*. Randomized phase III trial of prophylactic cranial irradiation versus observation in patients with fully resected stage IIIA-N2 non-small-cell lung cancer and high risk of cerebral metastases after adjuvant chemotherapy. Ann Oncol, 2015, 26: 504–509.

DOI 10.1007/s10330-015-0068-x
Cite this article as: Feng W, Fu XL. Role of radiation therapy in the management of stage III non-small cell lung cancers: current status and controversies. Oncol Transl Med, 2015, 1: 51–57.